

U.S.S.N: 10/027,982

Response to Advisory Action dated September 2, 2003

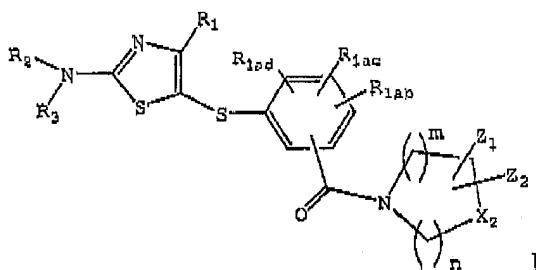
Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

Claims 1-6 (Canceled).

Claim 7 (Currently amended). A compound of formula I



diastereomers, enantiomers or salts thereof

where

R₁ is hydrogen or R₆;

R_{1ab} and R_{1ac} are independently hydrogen, R₆ or -OR₆;

R_{1ad} is hydrogen;

one of R₂ or R₃ is hydrogen or alkyl and the other R₂ or R₃ is -Z₄-R_{6a}, where: Z₄ is -Z₁₁-C(O)-Z₁₂-

and R_{6a} is phenyl substituted with Z₃;

R₆ is alkyl;

R₁, R_{1ab}, R_{1ac} and R_{1ad} are independently

(1) — hydrogen or R₆;

(2) — OH or -OR₆;

(3) — SH or -SR₆;

(4) — C(O)_qH, C(O)_qR₆, or -O-C(O)_qR₆, where q is 1 or 2;

(5) — SO₃H or -S(O)_qR₆;

U.S.S.N: 10/027,982

Response to Advisory Action dated September 2, 2003

- (6) —halo;
 (7) —cyano;
 (8) —nitro;
 (9) — $Z_4-NR_7R_8$;
 (10) — $Z_4-N(R_9)-Z_5-NR_{10}R_{11}$;
 (11) — $Z_4-N(R_{12})-Z_5-R_6$, or
 (12) — $P(O)(OR_6)_2$;

R_2 and R_3 are each independently H, Z_4-R_{6a} , or $Z_4-NR_{7a}R_{8a}$;

R_6 , R_{6a} , and R_{6b} are independently alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aralkyl, heterocyclo, or heterocycloalkyl, each of which is unsubstituted or substituted with Z_1 , Z_2 and one or more groups Z_3 ;

R_{7a} , R_{8a} , R_9 , R_{10} , R_{11} and R_{12}

- (1) are each independently hydrogen, or Z_4R_{6b} ; or
 (2) R_{7a} and R_{8a} may together be alkylene, alkenylene, or heteroalkylene, completing a 3- to 8-membered saturated or unsaturated ring with the nitrogen atom to which they are attached, which ring is unsubstituted or substituted with Z_1 , Z_2 and one or more groups Z_3 ; or
 (3) any two of R_9 , R_{10} and R_{11} may together be alkylene, alkenylene or heteroalkylene completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atoms to which they are attached, which ring is unsubstituted or substituted with one or more Z_1 , Z_2 and Z_3 ;

X_2 is CZ_{3a} , NZ_{3a} , O or S;

Z_{3a} is $-C(O)_qZ_{6a}$, where q is 1 H, hydroxy, optionally substituted alkyl, optionally substituted heterocyclo, optionally substituted aryl, optionally substituted aralkyl, OZ_6 , $-C(O)_qH$, $-C(O)_qZ_{6a}$, $-Z_4-NZ_7Z_8$, or $-Z_4-N(Z_{10})-Z_5-Z_6$;

n is 1 to 3 2;

m is zero to 2 1;

Z_1 and Z_2 are hydrogen;

Z_3 is $-Z_4-NZ_7Z_8$, where Z_4 is alkyl;

Z_1 , Z_2 and Z_3 are each independently

- (1) —hydrogen or Z_6 ;

U.S.S.N: 10/027,982

Response to Advisory Action dated September 2, 2003

- (2) ~~—OH or —OZ₆;~~
 (3) ~~—SH or —SZ₆;~~
 (4) ~~—C(O)_qH, —C(O)_qZ₆, or —O—C(O)_qZ₆, where q is 1 or 2;~~
 (5) ~~—SO₂H, —S(O)_qZ₆, or —S(O)_qN(Z₉)Z₆;~~
 (6) ~~—halo;~~
 (7) ~~—cyano;~~
 (8) ~~—nitro;~~
 (9) ~~—Z₄—NZ₇Z₈;~~
 (10) ~~—Z₄—N(Z₉)—Z₅—NZ₇Z₈;~~
 (11) ~~—Z₄—N(Z₁₀)—Z₅—Z₆;~~
 (12) ~~—Z₄—N(Z₁₀)—Z₅—I₁;~~
 (13) ~~—oxo;~~
 (14) ~~—any two of Z₄, Z₅, and Z₆ on a given substituent may together be alkylene or alkenylene completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached; or~~
 (15) ~~—any two of Z₄, Z₅, and Z₆ on a given substituent may together be —O—(CH₂)_q—O—;~~

Z₄ and Z₅ are each independently

- (1) ~~—a single bond;~~
 (2) ~~—Z₁₁—S(O)_q—Z₁₂;~~
 (3) ~~—Z₁₁—C(O)—Z₁₂;~~
 (4) ~~—Z₁₁—C(S)—Z₁₂;~~
 (5) ~~—Z₁₁—O—Z₁₂;~~
 (6) ~~—Z₁₁—S—Z₁₂;~~
 (7) ~~—Z₁₁—O—C(O)—Z₁₂;~~
 (8) ~~—Z₁₁—C(O)—O—Z₁₂;~~ or
 (9) ~~—alkyl~~

Z₆ and Z_{6a} is alkyl; are independently

- (i) ~~—alkyl, hydroxyalkyl, alkoxyalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aralkyl, alkylaryl, cycloalkylaryl, heterocyclo, or heterocycloalkyl;~~

U.S.S.N: 10/027,982

Response to Advisory Action dated September 2, 2003

- (ii) ~~a group (i) which is itself substituted by one or more of the same or different groups (i);~~
 or
 (iii) ~~a group (i) or (ii) which is independently substituted by one or more of the groups (2) to (15) of the definition of Z₄;~~

Z₇ and Z₈ are each independently hydrogen or -Z₄-Z_{6a}, where Z₄ is a single bond;

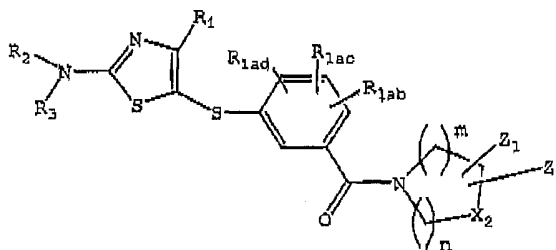
Z₇, Z₈, Z₉ and Z₁₀

- (1) ~~are each independently hydrogen or -Z₄-Z_{6a};~~
 (2) ~~Z₇ and Z₈ may together be alkylene, alkenylene, or heteroalkylene completing a 3 to 8 membered saturated or unsaturated ring together with the atoms to which they are attached, which ring is unsubstituted or substituted with one or more Z₁, Z₂ and Z₃; or~~
 (3) ~~Z₇ or Z₈, together with Z₉, may be alkylene, alkenylene, or heteroalkylene completing a 3 to 8 membered saturated or unsaturated ring together with the nitrogen atoms to which they are attached, which ring is unsubstituted or substituted with one or more Z₁, Z₂ and Z₃;~~

Z₁₁ and Z₁₂ are each independently a single bond.

- (1) ~~a single bond;~~
 (2) ~~alkylene;~~
 (3) ~~alkenylene, or~~
 (4) ~~alkynylene;~~

Claim 8 (Previously presented). A compound of claim 7 having the formula



Claim 9 (Currently amended). A compound of claim 8 where

R₂ is hydrogen or alkyl; and

R₃ is -Z₄R_{6a}, where: Z₄ is -C(O)- and R_{6a} is phenyl substituted with Z₃.

U.S.S.N: 10/027,982

Response to Advisory Action dated September 2, 2003

(a) ~~Z₄ is a single bond and R_{6a} is heteroaryl optionally substituted with one or more Z₁, Z₂ or Z₃;~~

(b) ~~Z₄ is C(O) and R_{6a} is~~

(1) ~~aryl optionally substituted with one or more Z₁, Z₂ or Z₃;~~

(2) ~~alkyl optionally substituted with one or more Z₁, Z₂ or Z₃;~~

(3) ~~cycloalkyl optionally substituted with one or more Z₁, Z₂ or Z₃; or~~

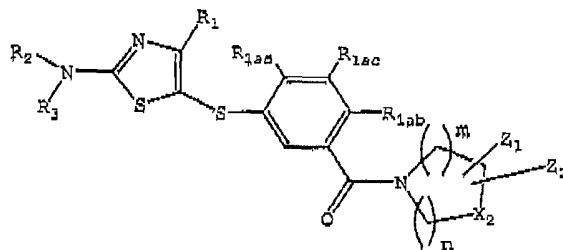
(4) ~~heterocycle optionally substituted with one or more Z₁, Z₂ or Z₃; or~~

(c) ~~Z₄ is C(O) O and R_{6a} is alkyl, cycloalkyl, aryl or aralkyl, any of which may be optionally substituted with one or more Z₁, Z₂ or Z₃.~~

Claim 10 (Currently amended). A compound of claim 9 wherein R_{1ab}[[L]] and R_{1ac} and R_{1ad} are independently H[[L]] or alkyl, hydroxy, nitro, halo, ~~OR₆, NR₇R₈, C(O)_qH or C(O)_qR₆.~~

Claim 11 (Original). A compound of claim 10 wherein R_{1ab} and R_{1ac} are independently alkyl.

Claim 12 (Currently amended). A compound of claim 8 having the following formula



where one of R_{1ab}[[L]] and R_{1ac} and R_{1ad} is H and the other is two are independently alkyl, hydroxy, nitro, halo, ~~OR₆, NR₇R₈, C(O)_qH, or C(O)_qR₆.~~

Claim 13 (Currently amended). A compound of claim 12 wherein one of R_{1ab}[[L]] and R_{1ac} and R_{1ad} is H and the other is two are independently alkyl or ~~OR₆.~~

Claim 14 (Previously presented). A compound of claim 13 wherein R_{1ac} is H.

U.S.S.N: 10/027,982
Response to Advisory Action dated September 2, 2003

Claim 15 (Canceled).

Claim 16 (Canceled)

Claim 17 (Previously presented). A pharmaceutical composition comprising at least one compound of claim 7 and a pharmaceutically acceptable vehicle or carrier therefor.

Claim 18 (Original). A pharmaceutical composition of claim 17 further comprising at least one additional therapeutic agent selected from anti-inflammatory agents, anti-proliferative agents, anti-cancer agents or anti-cytotoxic agents.

Claim 19 (Original). A pharmaceutical composition of claim 18 wherein the additional therapeutic agents are selected from steroids, mycophenolate mofetil, LTD₄ inhibitors, CTLA4-Ig, LEA-29Y, phosphodiesterase inhibitors, antihistamines, or p³⁸ MAPK inhibitors.

Claim 20 (Withdrawn). A method of treating a Tec family tyrosine kinase-associated disorder comprising the step of administering to a patient in need thereof, an effective amount of at least one compound of claim 1.

Claim 21 (Withdrawn). The method of claim 20 wherein the Tec family tyrosine kinase-associated disorder is an Emt-associated disorder.

Claim 22 (Withdrawn). The method of claim 21 wherein the Emt-associated disorder is selected from transplant rejection, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, lupus, graft vs. host disease, T-cell mediated hypersensitivity disease, psoriasis, Hashimoto's thyroiditis, Guillain-Barre syndrome, cancer, contact dermatitis, allergic disease, asthma, ischemic or reperfusion injury, atopic dermatitis, allergic rhinitis, or chronic obstructive pulmonary disease.

U.S.S.N: 10/027,982

Response to Advisory Action dated September 2, 2003

Claim 23 (New). A method of treating a Tec family tyrosine kinase-associated disorder comprising the step of administering to a patient in need thereof, an effective amount of at least one compound of claim 7.

Claim 24 (New). The method of claim 23 wherein the Tec family tyrosine kinase-associated disorder is an Emt-associated disorder.

Claim 25 (New). The method of claim 24 wherein the Emt-associated disorder is selected from transplant rejection, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, lupus, graft vs. host disease, T-cell mediated hypersensitivity disease, psoriasis, Hashimoto's thyroiditis, Guillain-Barre syndrome, cancer, contact dermatitis, allergic disease, asthma, ischemic or reperfusion injury, atopic dermatitis, allergic rhinitis, or chronic obstructive pulmonary disease.